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Abstract: BACKGROUND: The significance of the histological visualization of hemophagocytosis in tissues depends on the context, varying from a nonspecific phenomenon to a characteristic or diagnostic feature for certain disease entities. Hemophagocytosis is also one of the key features of macrophage activation syndrome (MAS) (hemophagocytic syndrome) a potentially life-threatening complication of underlying conditions such as infections, malignancy, and autoimmune disorders. Clinical manifestations of MAS are high fever, pancytopenia, liver dysfunction, and coagulopathy. These clinical symptoms are due to an abnormal activation of the immune system in a strong association with the cytokine milieu. The diagnosis of MAS may be easily missed; it is usually detected in the bone marrow, lymph node, liver, and spleen. Only few reports exist in the literature with histological description of cutaneous hemophagocytosis as a sign for MAS in patients with lymphoma and infection. In this report, the authors present the clinicopathological and immunohistochemical features of 3 patients with cutaneous hemophagocytosis, specifically erythrophagocytosis, associated with autoimmune disease, and discuss the relevance of these findings. OBSERVATION: The authors report 3 patients who developed cutaneous hemophagocytosis during the course of an underlying autoimmune disorder. One patient suffered from dermatomyositis, the other 2 patients from systemic lupus erythematosus, whereby one of them was a 3-month old girl with neonatal lupus erythematosus. The patient with dermatomyositis developed MAS according to the current diagnostic criteria. Although the 2 other patients had an acute flare of their autoimmune disease with histological signs of cutaneous hemophagocytosis, they did not fulfill the complete criteria for a diagnosis of MAS. Histiocyte proliferation and activation with increase of cytokines could be demonstrated by immunohistology. CONCLUSIONS: This report is the first to describe hemophagocytosis in cutaneous biopsies of patients with autoimmune diseases, associated with a complete or incomplete constellation of MAS. Key players in this process are histiocytes/macrophages engaged in phagocytosis of erythrocytes. Hemophagocytosis observed in skin biopsies may be a diagnostic clue for MAS and an indicator for a potentially aggressive course of the underlying disease.

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Hemophagocytosis in Cutaneous Autoimmune Disease

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Background: The significance of the histological visualization of hemophagocytosis in tissues depends on the context, varying from a nonspecific phenomenon to a characteristic or diagnostic feature for certain disease entities. Hemophagocytosis is also one of the key features of macrophage activation syndrome (MAS) (hemophagocytic syndrome) a potentially life-threatening complication of underlying conditions such as infections, malignancy, and autoimmune disorders. Clinical manifestations of MAS are high fever, pancytopenia, liver dysfunction, and coagulopathy. These clinical symptoms are due to an abnormal activation of the immune system in a strong association with the cytokine milieu. The diagnosis of MAS may be easily missed; it is usually detected in the bone marrow, lymph node, liver, and spleen. Only few reports exist in the literature with histological description of cutaneous hemophagocytosis as a sign for MAS in patients with lymphoma and infection. In this report, the authors present the clinicopathological and immunohistochemical features of 3 patients with cutaneous hemophagocytosis, specifically erythrophagocytosis, associated with autoimmune disease, and discuss the relevance of these findings.

Observation: The authors report 3 patients who developed cutaneous hemophagocytosis during the course of an underlying autoimmune disorder. One patient suffered from dermatomyositis, the other 2 patients from systemic lupus erythematosus, whereby one of them was a 3-month old girl with neonatal lupus erythematosus. The patient with dermatomyositis developed MAS according to the current diagnostic criteria. Although the 2 other patients had an acute flare of their autoimmune disease with histological signs of cutaneous hemophagocytosis, they did not fulfill the complete criteria for a diagnosis of MAS. Histiocyte proliferation and activation with increase of cytokines could be demonstrated by immunohistology.

Conclusions: This report is the first to describe hemophagocytosis in cutaneous biopsies of patients with autoimmune diseases, associated with a complete or incomplete constellation of MAS. Key players in this process are histiocytes/macrophages engaged in phagocytosis of erythrocytes. Hemophagocytosis observed in skin biopsies may be a diagnostic clue for MAS and an indicator for a potentially aggressive course of the underlying disease.

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The authors declare no conflicts of interest.

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INTRODUCTION

Hemophagocytosis is the process of engulfment of blood cells, in particular erythrocytes, by histiocytes through the cell-surface scavenger receptor CD163[1] and is a histological feature of selected diseases, including infections and malignancy. Hemophagocytosis is only rarely observed in the skin, and its significance is variable. It may be a characteristic well-known histological feature of certain entities such as primary cutaneous γ/δ T-cell lymphoma, intravascular large B-cell lymphoma, or Rosai–Dorfman disease, but it may also represent a nonspecific phenomenon, for example, in the late stage of hemorrhagic disorders. When hemophagocytosis arises in the context of systemic symptoms, it may also be a key feature indicative of a severe and potentially life-threatening condition characterized by a hyperactivation of the immune system and excessive secretion of cytokines. This syndrome has been reported under different names in the literature, including hemophagocytic syndrome and secondary hemophagocytic lymphohistiocytosis, and it belongs to the spectrum of macrophage associated histiocytoses[2,3]; the primary or familial form is a genetic disorder with mutations in the perforin gene or in genes implicated in the exocytosis of cytotoxic granules from cytotoxic T lymphocytes.[4] The secondary form occurs as a severe complication of an underlying disorder and was first reported in patients with different types of infection[5] and malignancies, lymphomas in particular.[6] Macrophage activation syndrome (MAS) is the term applied for hemophagocytic syndrome occurring in the context of autoimmune disease. In 1991, Wong et al[7] reported patients with active systemic lupus erythematosus, whose bone marrow biopsies revealed hemophagocytosis. Since then, MAS has been reported in the context of several autoimmune diseases including systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, progressive systemic sclerosis, and mixed connective tissue disease.[8–13] It has also been observed in Still disease, a disorder now recognized to belong to the group of auto-inflammatory diseases involving a dysregulation of the innate immune system.[14,15]

The clinical symptoms of MAS are due to an uncontrolled and excessive activation of the immune system with a proliferation of stimulated histiocytes and lymphocytes and enhanced secretion of pro-inflammatory cytokines such tumor necrosis factor alpha (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6), and IL-1β.[16] This cytokine storm leads

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TABLE 1. Diagnostic Guidelines for Macrophage Activation System Complicating Systemic Juvenile Idiopathic Arthritis

Laboratory criteria
Decreased platelet count ($\leq 262 \times 10^9$/L)
Elevated levels of aspartate aminotransferase (>59 U/L)
Decreased white blood cell count ($\leq 4.0 \times 10^9$/L)
Hypofibrinogenemia (≤2.5 g/L)
Clinical criteria
Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
Hemorrhages (purpura, easy bruising, mucosal bleeding)
Hepatomegaly (≥3 cm below the costal arch)
Histopathological criterion
Evidence of macrophage hemophagocytosis in the bone marrow aspirate

The diagnosis of MAS requires the presence of any 2 or more laboratory criteria or of any 2 or 3 or more clinical and/or laboratory criteria.

Adapted from Ravelli et al. *J Pediatr.* 2005.[16,17] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

to a sepsis-like clinical presentation with high fever, hepatosplenomegaly, cytopenia, disseminated intravascular coagulation, and neurological symptoms. Characteristic laboratory findings of MAS include anemia, and thrombocytopenia, hypofibrinogenemia, elevation of ferritin, and liver enzymes. Hemophagocytosis in different organs is an important criterion for the diagnosis of MAS, although its presence or the proof of its existence is not mandatory for establishing the diagnosis. Specific diagnostic criteria for MAS have been suggested[17,18] and are summarized in Table 1.

We demonstrate for the first time hemophagocytosis (erythrophagocytosis) in skin specimens of 3 patients with autoimmune disease. One patient with dermatomyositis showed acute and severe aggravation of his illness and fulfilled the criteria for the diagnosis of MAS. In 2 patients with systemic lupus erythematosus, hemophagocytosis in the skin was not associated with the full clinical presentation of MAS.

FIGURE 1. Patient 1. Autoimmune hemophagocytic syndrome. A 62-year-old man with dermatomyositis complicated by MAS. Excessive swelling, violet color, hemorrhage, and crusting of the eyelids and the periorbital region.

OBSERVATIONS

Clinical Findings

Patient 1

A 62-year-old patient presented with high fever, lethargy, muscle weakness, excessive edema with violaceous discoloration, echymosis, ulceration and crusting of the periorbital regions (Fig. 1). Gottron papules were obvious over knuckles and interphalangeal joints. Internal investigations and laboratory tests revealed: elevation of muscle and liver enzymes, pancytopenia, splenomegaly, lymphadenopathy, elevated ferritine, and hypertriglyceridemia.

Electromyography showed signs of myositis. Bone marrow biopsy failed to exhibit macrophage proliferation and hemophagocytosis. Based on these findings together with the skin biopsy (see below), a diagnosis of dermatomysitis complicated by MAS was made. The general condition of the patient deteriorated rapidly, and he died a few days after hospital admission.

Patient 2

A 29-year-old woman with long standing systemic lupus erythematosus displayed annular and polycyclic lesions with scaly borders on the trunk and extensor surfaces of the arms (Fig. 2). In addition, a butterfly rash on the face and nail fold erythema could be observed. She complained also of fatigue and joint pain. Laboratory tests revealed positive results for antinuclear antibodies, anti-dsDNA

FIGURE 2. Patient 2. Systemic lupus erythematosus showing annular and polycyclic lesions with a scaly border on the arm.

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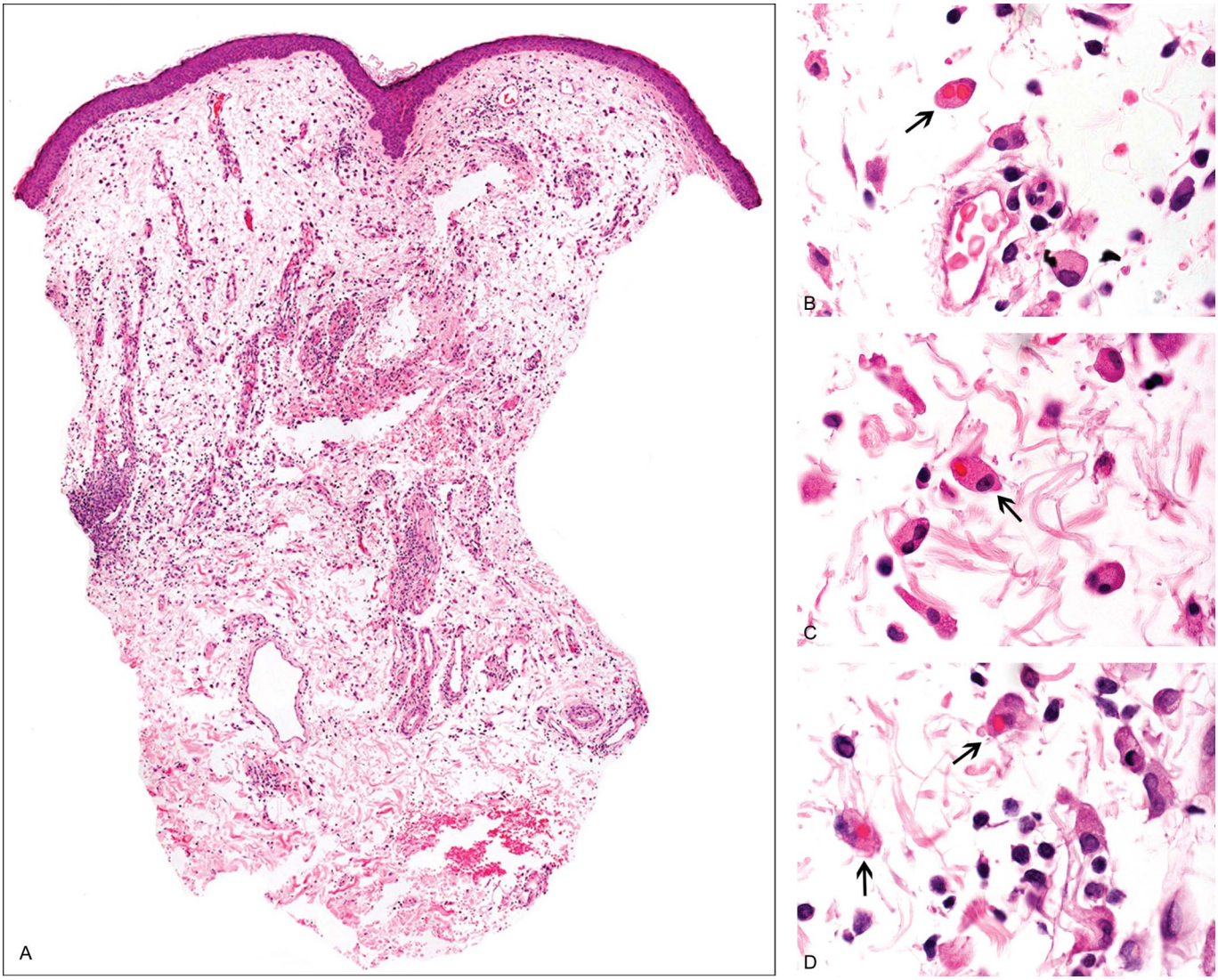

FIGURE 3. Patient 1. A, Periorbital biopsy. Increased number of histiocytes/macrophages in edematous dermis. B and C, Arrows indicate macrophages ingesting erythrocytes (hemophagocytosis).

antibodies, anti-Ro/SSA antibodies, proteinuria, and low serum complement levels.

Patient 3

A 3-month-old girl presented with disseminated reddish-brown lesions on the head and trunk. Periorbital scaly erythematous confluent patches were also observed ("raccoon eye" appearance). Other relevant findings were antinuclear antibodies, anti-Ro/SSA, and anti-La/SSB positive; atrioventricular heart block, first degree. Diagnosis was neonatal lupus erythematosus.

Histological and Immunohistological Findings

Skin biopsy specimens were embedded in paraffin and Hematoxilin-Eosin-staining was performed. In addition, the following markers used for the assessment of monocyte–macrophage activation were studied: CD163 (for M1 and M2, macrophage subpopulations, Leica, clone 10D6 Germany), TNF-α (R&D Systems, mouse monoclonal, clone 28401, England, United Kingdom), IFN-γ (rabbit polyclonal; Abcam, England, United Kingdom), IL-6 (rabbit polyclonal; Abcam), and IL-1β (rabbit polyclonal; Abcam) were performed in the skin biopsies of patients 1 and 2.

Patient 1

A biopsy from the periorbital region revealed focally smudged appearance of the dermoepidermal junction, massive edema in the upper dermis, plenty of erythrocytes, proliferation of vessels, and an infiltrate predominated by histiocytes/macrophages with fewer lymphocytes. Most notable was that a considerable number of the macrophages displayed erythrophagocytosis (Figs. 3A–D).

A second biopsy from a Gottron papule on the left dorsal hand showed hyperkeratosis, basal vacuolar changes and a thickened basement membrane, a few dyskeratotic keratinocytes, ectatic vessels, and a sparse superficial inflammatory infiltrate.

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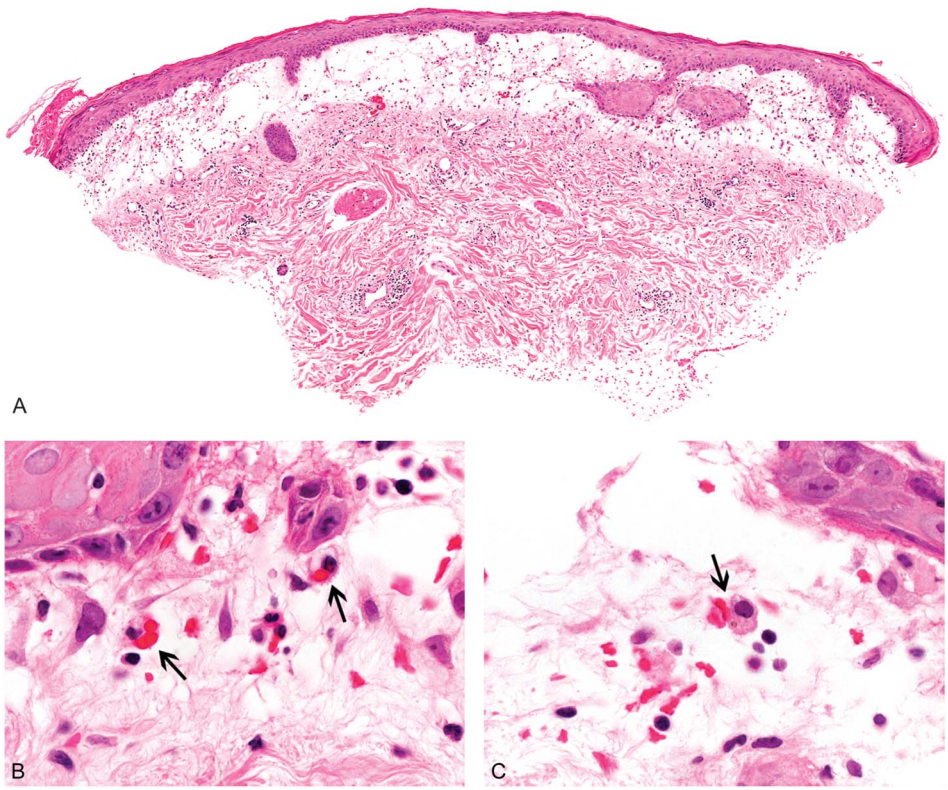

FIGURE 4. Patient 2. Biopsy from the arm. A, Markedly edematous papillary dermis with proliferation of histiocytes and extravasated erythrocytes. B and C, Arrows indicate hemophagocytosis. Note apposition of erythrocytes to macrophage in Fig. 4C.

Patient 2

A biopsy from the left arm showed characteristic epidermal changes of lupus erythematosus. Striking features were a marked edema in the upper dermis with hemorrhage and numerous macrophages engaged in phagocytosis of erythrocytes (Figs. 4A–C).

Imunohistochemical analysis [performed in patient 1 on the face biopsy (Fig. 5A), patient 2 on the arm biopsy] revealed numerous CD163-positive macrophages within the upper dermis. In addition, a high expression of IL-6, TNF-α, IFN-γ, and IL-1β could be detected in these cells.

Patient 3

A biopsy from the trunk featured a thinned epidermis with scale crusts, basal vacuolar alteration, necrotic keratinocytes, dermal edema, erythrocyte extravasation, and lymphohistiocytic infiltrates with neutrophils. Again, most remarkable was the identification of macrophages containing phagocyted red blood cells.

DISCUSSION

Here, we describe the clinical, histopathological, and immunohistochemical features of 3 patients with cutaneous hemophagocytosis in the context of underlying autoimmune disease (systemic lupus erythematosus and dermatomyositis), associated with MAS in 1 case.

Hemophagocytosis is a phenomenon that is only rarely observed in the skin, and its significance is dependent on the clinicopathological context. It is a hallmark feature of MAS, a potentially life-threatening syndrome complicating malignancies, infections, and autoimmune disease.

Although hemophagocytosis is typical for MAS, its mere presence is not automatically synonymous with MAS. Hemophagocytosis may be absent in MAS and Hemophagocytic syndrome, especially in the initial stages. However, it may occur as a nonspecific phenomenon in various context as blood transfusions, infection, autoimmune disease, and other causes of red blood cell destruction. Recently, 2 articles reported perivascular hemophagocytosis with signs of vasculitis in skin biopsies of patients without the full clinical presentation of MAS. The authors discuss the possibility of hemophagocytosis as a sign of incomplete MAS versus it being simply a nonspecific sign of leucocytoclastic vasculitis.[19,20]

In our patients, the skin biopsies were performed at the moment of an acute flare in the activity of their underlying autoimmune disease. One of the patients was then diagnosed with MAS; the finding of hemophagocytosis in the skin biopsy of this patient was an important additional clue to the diagnosis.

The significance of the finding of hemophagocytosis in the skin biopsies of our 2 patients with systemic lupus erythematosus, who did not have all criteria required for the classification as MAS is more difficult to evaluate. It might be interpreted as a sign of disease activity as it was associated with a flare. Further observations are required to clarify the significance of the cutaneous hemophagocytic process in autoimmune disease without full clinical evidence of MAS.

Interestingly, a proliferation of a significant number of CD163-positive histiocytes/macrophages could be demonstrated

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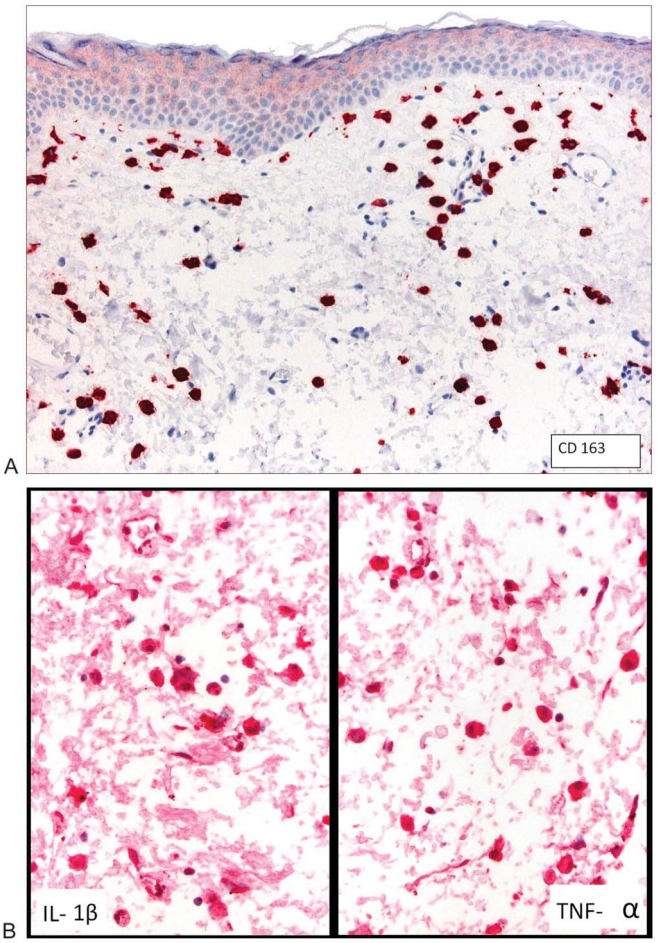

FIGURE 5. Immunohistological analysis. A, High proportion of CD163-positive activated histiocytes/macrophages (patient 1). B, Strong expression of IL-1β and TNF-α in histiocytes/macrophages (patient 2).

within the dermis. CD163 is a hemoglobin–haptoglobin scavenger receptor and a lineage specific marker for histiocytes in MAS. The soluble form of CD163 has been identified as a potential marker for the diagnosis of MAS.[1]

We also analyzed the pattern of cytokine expression in the skin biopsy specimens of our patients 1 and 2 and found overproduction of cytokins such as TNF-α, IFN-γ, IL-6, and IL-1β, showing evidence of activation of histiocytes. These cytokines have been demonstrated to play a crucial role in the pathogenesis of MAS[16] and can induce hemophagocytosis.

In conclusion, this is the first description of hemophagocytosis in skin biopsies of patients with autoimmune diseases, delivering also evidence on the involvement of cytokine-producing activated macrophages. The diagnosis of MAS is often challenging and may be delayed or even missed because of the fact that there may be overlapping clinical features with the underlying autoimmune disorder. The presence of hemophagocytosis, without being specific or mandatory for the diagnosis of MAS, is a very important clue and is usually observed in biopsies of lymphoid tissues. However, hemophagocytosis observed in skin biopsies can also be a sign of MAS. Demonstration of hemophagocytosis in skin biopsies may help to establish the diagnosis of MAS and also potentially indicate a more severe course of the underlying disorder. It should also provide new insights in the mechanisms of host defense and the pathogenesis of autoimmune disease.

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